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Full Paper

INTENSIFICATION OF CONTINUOUS ORTHO-LITHIATION AT AMBIENT CONDITIONS – Process Understanding and Assessment of Sustainability Benefits

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INTENSIFICATION OF CONTINUOUS ORTHO-LITHIATION AT AMBIENT CONDITIONS – Process Understanding and Assessment of Sustainability Benefits

Ruili Feng,^{a,b} Sushil Ramchandani,^b Balamurugan Ramalingam,^c Song Wei Benjamin Tan,^b

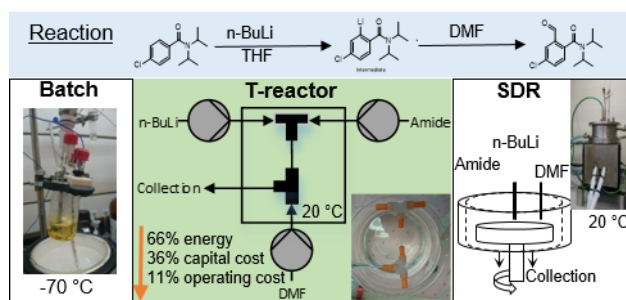
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KEYWORDS Process intensification, lithiation, sustainability, spinning disc reactor, continuous processing, microreactor

ABSTRACT The feasibility of performing an ortho-lithiation reaction in a T-reactor and a Spinning Disc Reactor (SDR) at ambient temperature has been demonstrated and compared experimentally to a conventional batch stirred tank reactor (STR) process performed at a cryogenic temperature of -70 °C. Benefits of significantly improved mixing and much shorter residence times in the flow reactors eliminated the need for cryogenic cooling in batch processing which is a costly requirement. A theoretical evaluation of a scaled up process with a design product output of 3 tons per year highlights that significant process intensification is achievable in the flow reactors which demonstrate higher energy efficiency, better volume efficiency, smaller processing inventory and smaller equipment footprint. For this reaction, the performance of the T-reactor is the best among the three reactors leading to much lower reactor investment and operating cost. The SDR was also demonstrated to be effective, even though this reaction did not take advantage of its inherent capabilities in solids handling or rapid heat removal through evaporation/gas disengagement, all of which present major challenges in enclosed channels geometries such as the T-reactor.

1. Introduction

Ortho-lithiation is an important class of reaction for the synthesis of regiospecifically substituted aromatics and it is an emerging method to prepare phthalides which are common pharmaceutically active compounds.¹⁻⁶ Ortho-lithiation is typically conducted in batch mode

under cryogenic temperatures (-78 to -40 °C)⁷ to minimize the side reactions arising from the highly reactive organolithium intermediates. The challenges of safely handling both the highly reactive chemicals and a highly energetic reaction in scaled-up operations constitute a major disadvantage of such batch processes. One solution to overcome these safety related issues is to implement continuous flow processes.⁸

Indeed, several successful studies have been performed to scale up continuous lithiation using tubular flow reactors.^{4, 6} These flow reactors offer superior control of process parameters like mixing, residence time and temperature. There are examples of deploying flow processing for lithiation reaction as a process intensification (PI) technique. The Yoshida group demonstrated several lithiation reactions using different electrophiles in microstructured flow devices (consisting of micromixers and microtube reactors) to be superior to batch protocols.⁹⁻¹³ Roberge and co-workers⁵ and Stephan and co-workers⁴ have both demonstrated the possibility to scale up lithiation reactions in flow reactors for pharmaceutical manufacturing. However, both authors reported challenges in handling plugging due to precipitation of salts. Kockmann and co-workers¹⁴ evaluated the feasibility to scale up the lithiation reaction using tubular flow reactors with different channel diameters and flow rates to avoid parallelization.

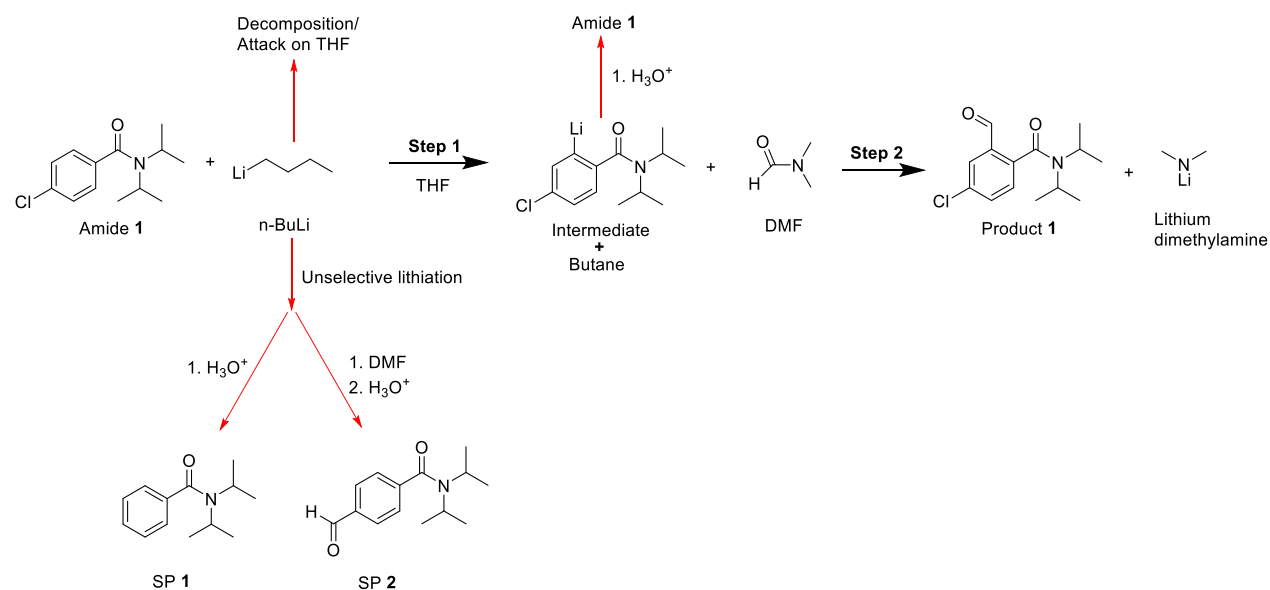
One major problem with adopting flow processing in enclosed microchannels is the possibility of deposition of the intermediate lithium salts, which can lead to clogging of such flow reactors.⁴ We envision overcoming this limitation by the use of the SDR which allows a free surface film flowing over the disc surface instead of through an enclosed channel. The SDR also possesses a number of characteristics which make it a potential intensification tool for ortho-lithiation reaction, such as the capability of achieving rapid mixing with an estimated micromixing time in the range of 0.125 to 0.02 s¹⁵ and high mass and heat transfer rates in the free flowing thin film

of liquid produced owing to centrifugal acceleration created by rotation.¹⁶ Various examples in the literature demonstrate the advantages of performing fast reactions in the SDR.¹⁷⁻¹⁹ Inspired by these advantages, the feasibility of performing the ortho-lithiation reaction was demonstrated.

The objective of this work is to evaluate the sustainability benefits of operating ortho-lithiation reaction in different process intensification (PI) reactors as compared to the conventional batch reactor.²⁰ In this work we focus on comparing the sustainability performance of a batch and two intensive continuous reactors (the T-reactor and the spinning disc reactor), for the reaction step excluding workup at a hypothetical design scale of 3 tons per year. The potential benefits that could be achieved are higher reaction selectivity and material efficiency, lower energy consumption, improved safety and economic savings.

2. Experimental work

2.1. Reaction system



Scheme 1. Reaction used in this study and possible side reactions.

1
2
3 A typical ortho-lithiation reaction is taken from the literature (Scheme 1),² where the 4-chloro-
4 N,N-diisopropylbenzamide (amide **1**) is treated with n-Butyllithium (n-BuLi, 1.6 M in hexane) in
5 tetrahydrofuran (THF) at -70 to -75 °C and the lithiation occurs selectively at the ortho-position
6 to the amide group. The subsequent treatment with dimethylformamide (DMF) in Step 2
7 produces 4-chloro-N,N-diisopropyl-2-formylbenzamide (product **1**). Step 1 is a very fast reaction
8 with an adiabatic temperature rise of more than 55 °C (230 kJ/mol n-BuLi).²¹ The second step is
9 less demanding in terms of heat exchange and mixing and has a lesser possibility for new side
10 product formation.¹⁴

11
12 Unfortunately the side reaction mechanism of ortho-lithiation is not yet fully understood. Only
13 partial information was obtained in our study using Liquid Chromatography-Mass Spectrometry
14 (LC-MS) which nevertheless provided some useful insight into the possible side products
15 formed. As shown in Scheme 1, two possible side reactions have been proposed based on
16 identification by LC-MS of two molecular masses which have been matched to our anticipated
17 molecular structures SP **1** and SP **2**. It is to be noted that versions of other structural isomers of
18 these molecules are also possible. It is postulated that these side products arise from unselective
19 lithiation reactions competing with the desired ortho-lithiation in Step 1. The mixing
20 performance in Step 2 determines the formation of either SP **1** or SP **2**. Poor mixing in Step 2
21 tends to generate SP **1** as DMF fails to react with the lithiated species before contacting water,
22 while good mixing in Step 2 allows the lithiated species to undergo electrophilic addition to form
23 SP **2**. Certain processing conditions may also affect the overall amide conversion. For instance,
24 n-BuLi tends to decompose or get consumed in the reaction with THF²² when n-BuLi is not well-
25 mixed. A lesser quantity of n-BuLi available for reaction with amide **1** leads to low overall
26 conversion. Similarly low overall conversion is expected when the DMF fails to mix

homogeneously with the reaction mixture in Step 2, so the intermediate is converted back to amide **1** upon contact with water during separation process.

Three types of reactors were evaluated for sustainability comparisons:

- 1) Batch stirred-tank reactor (STR) under cryogenic conditions – conventional manufacturing process.
- 2) T-reactors operating in flow at ambient temperature – similar to microreactor but with larger channel diameters to avoid clogging.
- 3) Spinning disc reactor (SDR) in flow at ambient temperature – giving a very different mode of mixing and operation from the T-reactor.

2.2. Experimental procedures

For the stirred tank reactor, a 50 mL Multi-max™ reactor (with standard overhead stirrer, 2 blade propeller impeller with diameter of 2.5 cm) was employed to conduct the ortho-lithiation reaction over a range of temperatures between -75 °C and 20 °C and impeller agitation speed between 50 to 400 rpm. A total of 2 g (8 mmol) of amide **1** was added into the reactor followed by 19 g of solvent, THF (anhydrous, 99.8%). The n-BuLi in hexanes (1.6 M, 1.2 mole equivalent) was added dropwise (0.4 mmol/min) via syringe pump (NE 1000) to the solution of starting material in THF in the reactor. The reactor was submerged in an isopropyl alcohol (IPA) bath with constant addition of dry ice to maintain reactor internal temperature at about -70 °C monitored using a digital temperature sensor in contact with the reaction mixture. After which the reaction mixture was allowed to warm to about -50 °C when DMF (0.8 g, 11 mmol, 1.3 mole equivalent) was added via syringe pump (NE 300). During the reaction, an inert reaction environment was maintained under argon blanket.

The preparation steps for both the T-reactors and the SDR were similar. 0.4 M of amide **1** solution was prepared by dissolving amide **1** (24 g) in THF using a 250 mL volumetric flask. About 120 mL of the amide **1** solution, 40 mL of n-BuLi in hexanes (1.6M) and 10 mL of DMF were drawn using syringes (HSW syringes) and loaded onto syringe pumps (NE 1010 dual, NE 1000, NE300 respectively). Special care was taken to ensure the drawing of n-BuLi into the syringe was not exposed to air. The T-reactor was flushed and filled with anhydrous THF for at least 10 minutes before experiments to ensure an anhydrous environment. Similarly for SDR, the reactor was purged with argon prior to the experiment and kept under positive argon pressure throughout experiment. The collected solution was sent to waste for the first 30 s to allow the system to reach steady state. After this time the output of the reactor was collected in fixed time interval of about every 30 s. However, due to limited volume of the syringe, the flow reactors could only be operated for a short time (about 5 minutes). Samples were taken at different time intervals to ensure steady state has been reached.

The T-reactor was assembled in house from commercially available PTFE tubing (Sigma Aldrich, 1.6 mm I.D.) and connected to of two PTFE T-mixers (Upchurch Scientific P-713, 1.25 mm I.D., 17.5 μ L swept volume). The T-reactor setup, included a reactor tubing, R1, ranged from 0.06 to 2 m. The n-BuLi in hexanes and the amide **1** in THF streams were pumped into the first T-mixer from opposite directions and the DMF stream merged with the reaction mixture in the second T-mixer. Other than the syringe pumps and the outlet tubing, the T-reactor was immersed in a circulated silicone oil bath using Huber temperature control unit.

For the SDR, the stainless-steel disc of 10 cm in diameter was driven by an electric motor which operates in the range of 400-2,400 rpm. The SDR was tightly enclosed and purged with argon prior to the experiment and kept at positive argon gas pressure throughout the experiment.

Cooling water was recirculated underneath the disk surface through a temperature-controlled water bath to keep the disc temperature constant. The three reagents were delivered via syringe pumps onto the rotating disk through three feed pipes. The two center feed pipes delivering amide **1** in THF and n-BuLi in hexanes were located at the center of the disc. The third feed pipe delivering DMF was located at a radial distance of 45 mm from the center of the disc. All the feed pipes were fixed at a distance of 5.0 mm above the surface. The feed tube diameter was approximately 1.6 mm for the starting material stream and 1.0 mm for the n-BuLi in hexanes and DMF streams where the flow rates were slower. The reactor diagram is depicted in Figure 1.

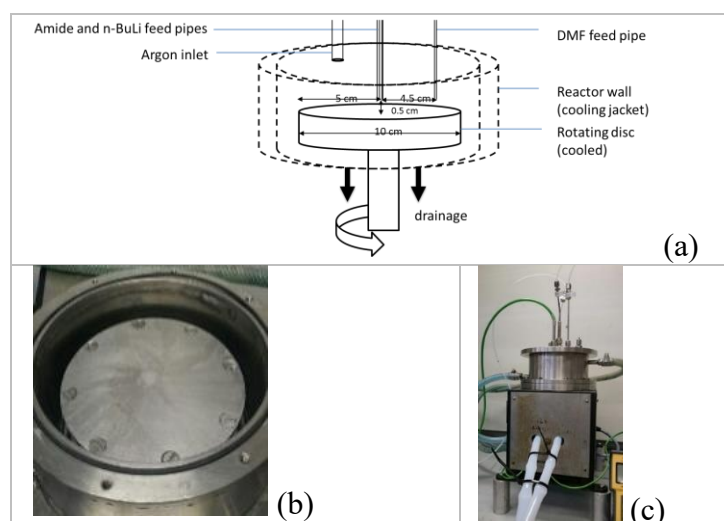


Figure 1 (a) Schematic of the SDR (10 cm diameter) set-up; (b) view of disc surface; (c) picture of the set-up.

The n-BuLi (~1.6 M solution in hexanes) was titrated once a week.²³ It is noted that the concentrations of the n-BuLi may vary (1.4-1.6 M). To account for the variation in n-BuLi concentration, the corresponding n-BuLi flow rates were adjusted.

2.3. Method of analysis

The internal standard method was used to analyze samples collected at fixed time intervals. The product **1** yield and overall conversion were determined by Gas Chromatography (GC) using Agilent (GC 6890N) GC-FID equipped with HP-5 column. Response factors of the product **1** and amide **1** were determined by calibration using n-hexadecane as the internal standard.

LC-MS analysis was done at ambient temperature via reverse phase liquid chromatography with Tandem Mass Spectrometry (Waters Quattro Micro API TM LCMS/MS) with Restek Ultra C8 column (5 μ m, 4.6 mm (ID), 150 mm (L)) an isocratic elution gradient of 50% acetonitrile/water was used. The samples were ionized by ESI and the ionized components were analysed by a quadrupole analyzer. Retention time of amide **1** is 27 min; product **1** is 19 min; SP **1** is 15 min; SP **2** is 10 min.

3. Results and discussions

3.1. Development of stirred-tank reactor (STR) batch process

3.1.1. Effect of temperature

Temperature is one of the most important process parameters in for ortho-lithiation reaction in batch process. Attempts were made to perform the reaction at higher temperatures but side products were formed in large extend as shown in Table 1, the drastic drop in yield. As expected, -70 °C is necessary for reaction in stirred tank reactor. In large scale batch production, the addition rate of n-BuLi should be adjusted to maintain the reaction temperature below -70 °C.

Table 1 Ortho-lithiation at different temperatures at constant agitation speed of 400 rpm in batch process.

Temperature (°C)	Product 1 yield (%)	Overall conversion (%)	Impurity* (%)
20	3	93	90

0	26	99	73
-20	36	97	61
-70	96	99	3

(*) % impurity = % overall conversion - % product 1 yield

3.1.2. Effect of agitation speed

Mixing is also very important for ortho-lithiation which is a fast reaction. As seen in Table 2, the results are very dependent on mixing. Poor mixing not only lead to increase in impurities but also lower overall conversion. The low agitation speed was expected to lead to a high n-BuLi localized concentration due to ineffective mixing which might encourage decomposition and/or attack on THF.²² The loss of n-BuLi is evident from the low consumption of amide **1** as seen in Table 2 at agitation speeds of 50 and 100 rpm.

For the Multi-max™ reactor used, the maximum agitation speed achievable was 400 rpm. This corresponds to a power dissipation of 0.053 W/kg which is set as the minimum power dissipation for batch large scale production

Table 2 Ortho-lithiation at 0 °C under different agitation speeds where n-BuLi and DMF addition rates were kept constant at 0.4 and 2 mmol/min respectively.

Agitation (rpm)	Product yield (%)	Overall conversion (%)	Impurity* (%)	Power (W/kg)
400	26	99	73	0.053
200	25	99	74	0.007
150	22	98	76	0.003
100	7	42	35	0.0008
50	7	36	29	0.0001

(*) % impurity = % overall conversion - % product 1 yield

3.1.3. Effect of DMF addition mode in Step 2

To study the effect of mixing on Step 2, two different DMF addition rates were used while keeping the agitation speed of the reactor constant at 400 rpm (Table 3). The high charging rate of DMF might have caused inhomogeneous mixing and hotspot formation that could lead to decomposition of the intermediates, where some of the lithiated intermediates might have been converted back to amide **1**. This explains the lower overall conversion of amide **1** at fast DMF dosing rate. The product in the crude reaction mixture (after DMF addition) is relatively stable for up to 1 hour prior to the work-up process.

Table 3 Addition mode of DMF at -50 °C (Step 1 performed at -70 °C)

DMF addition rate	Product 1 yield (%)	Overall conversion (%)	Impurity* (%)	Agitation speed (rpm)
One shot (~10 mmol/s)	30	63	33	400
Usual dosing rate (2 mmol/min)	96	99	3	400

(*) % impurity = % overall conversion - % product **1** yield

3.2. Development of T-reactor flow process

3.2.1. Effect of DMF addition mode in Step 2

The addition mode/mixing of DMF in Step 2 plays an important part in determining the overall product **1** yield and overall amide **1** conversion. It is evident from Table 4 that the DMF flow rate can influence the product **1** yield. Beyond a ‘minimum’ DMF quantity, the mixing limitation in Step 2 diminishes and reaction profile depends solely on the flow conditions in Step 1. However, the ‘minimum’ DMF quantity is likely to be a variable which is dependent on Step 1 flow rate.

For simplicity of scale up and material efficiency, DMF of 2 mole equivalent with respect to amide **1** was used in all flow experiments. For T-reactor, the same mixing principles in Step 1

can be applied to Step 2 as the reaction mixture meets ‘head on’ with the DMF feed in the second T-mixer. The speeds of the feeds in the second T-mixer mixing channel are dependent on the combined flow speed in the first T-mixer. Thus, it is expected that mixing time in the second T-mixer is of similar order of magnitude as the first T-mixer. Therefore, good mixing performance in the first T-mixer is likely to improve mixing in the second T-mixer. It is also noted that poor reaction performance could be a result of poor mixing contributed by both steps.

Table 4 Experiments using different quantities of DMF carried out under constant Step 1 residence time of 0.4 s and bath temperature set at 17 °C.

Run	DMF flow rate (mL/s)	DMF mole ratio to amide 1	Step 1 combined flow rate (mL/s)	Step 2 combined flow rate (mL/s)	Product 1 yield (%)	Overall conversion (%)	Impurity* (%)
1	0.01	1.3	0.65	0.66	74	97	23
2	0.02	1.7	0.65	0.67	90	99	9
3	0.03	2	0.65	0.68	92	99	7
4	0.05	4	0.65	0.70	91	99	8
5	0.08	6	0.65	0.73	90	99	9
6	DMF reservoir	~ unlimited	0.65	NA	91	99	8

(*) % impurity = % overall conversion - % product 1 yield

3.2.2. Effect of circulation bath temperature

Attempts were made to change the reaction temperature of the T-reactor by adjusting the bath temperature. Figure 2 shows that the reaction seemed robust over a range of bath temperature from 0 °C to 40 °C. Assuming that the system is adiabatic as PTFE is a good insulator, the temperature rise is expected to be more than 50 °C and yet there was no significant deterioration in product 1 formation observed in Figure 2. This is referred to as Flash Chemistry²⁴⁻²⁵ where reaction is usually completed in less than a second coupled with highly efficient mixing. For this

type of condition, the mixing performance is more important than temperature control as the residence times are very short so side reactions due to temperature rise become less importance. If this is true, then the poor heat transfer capability of the T-reactor may be compensated by improving the mixing performance and shortening the residence time. The thermal stabilities of the product **1** and amide **1** up to 300 °C were determined using differential scanning calorimetry (DSC) and no secondary decomposition is observed. However, it was difficult to conduct thermal stability test on the intermediate as they are unstable and decompose instantaneously in air. The circulated silicon bath temperature was maintained at 17 °C for subsequent experiments.

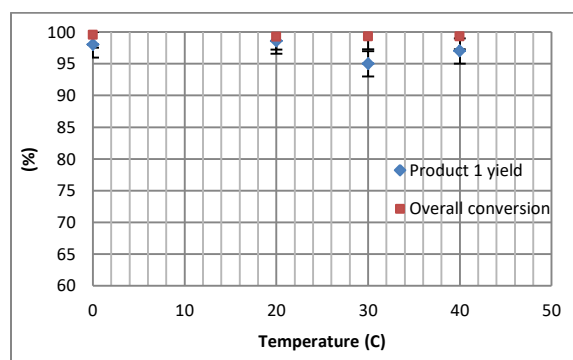


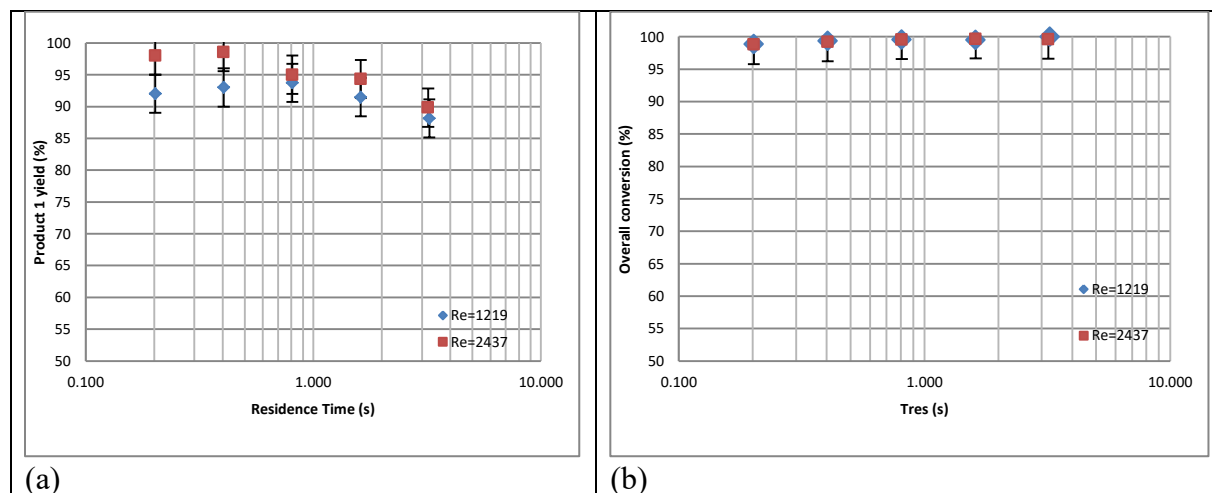
Figure 2 Effect of circulation bath temperature on Step 1 under constant residence time (0.4 s) and combined flow speed.

3.2.3. Effect of residence time in Step 1

Figure 3 shows the effect of residence time for two different flow speeds and it is demonstrated that shorter Step 1 residence time improves the product **1** yield. The longer than desired residence time could result in poorer yield due to prolonged exposure to high temperature which might cause decomposition of intermediate or overreaction.

One observation made from Figure 3 (a) is that the gap in product **1** yield between Reynolds numbers (Re) of 1219 and 2437 appears more significant at shorter residence times. One possible reason could be the effect of mixing limitation is more prominent at low flow speed (Re=1219)

and short residence times (below 0.8 s). As the residence time increases for Re of 1219, there is a subtle improvement in product **1** yield as there is more time available for mixing to occur until over-reaction kicks in as characterized by the drop in yield. Therefore, the optimum residence time is very much mixing dependent.



3 (a) Product 1 yield and; (b) overall conversion against residence time (Step 1) in first T-mixer for different Re numbers of 1219 and 2437.

3.2.4. Effect of flow speed in Step 1

Figure 4 shows the effect of flow speed in Step 1 on reaction profile for two different residence times, at 0.4 s and 0.8 s. The range of Reynolds number achieved in the T-mixer mixing channel varies from 300 to 9800. The geometry of the T-mixer stays constant for various Re but the subsequent PTFE tube that connects to the T-mixer outlet varies in length to maintain constant overall residence time.

In the regime where Reynolds number is lower than 2400, the reaction is mixing controlled as the flow in the pipeline is likely to be laminar where the velocity vectors are parallel and there is little radial mixing. These laminar flows introduce gradients in reagent concentrations and temperature as the reaction between n-BuLi and amide **1** occurs in the interface of the two parallel streams due to molecular interaction arising from diffusion. The bulk of amide **1**

remains unreacted as the two reagents are not homogeneously mixed while the rest of the n-BuLi gets consumed by reacting unselectively with THF and DMF that are present in abundance. This explains the low overall conversion at the lowest flow rate. As flow speed increases, it is likely that the flow in the T-mixer transitions towards turbulence and the resulting enhanced mixing of the two fluid streams generates increased contact area, higher product **1** yield (Figure 4 (a)) and overall conversion (Figure 4 (b)).

Under the same flow speed as in the mixing limited regime, longer residence time provides more time for mixing/diffusion which could result in higher overall conversion. This is evident at Re 609 where the overall conversion at 0.8 s is clearly higher than that at 0.4 s. As Re increases, the corresponding mixing limitation diminishes and the benefit of having longer residence time becomes negligible as the overall conversion approaches 100%. An optimum yield/selectivity is obtained at Re 2437 as the product **1** yield/selectivity at 0.4 s surpasses that at 0.8 s and this could be the tipping point where the controlling factor transits from mixing to residence time.

As the Re increased beyond 2400, the product **1** yield/selectivity reached a plateau or is slightly decreased. One possible reason could be the back-mixing effect in the n-BuLi feed arm as the amide **1** feed speed is more than three times higher than the n-BuLi. The pressure difference between the feed inlets gets more severe as flow speed increases. Back-mixing could cause more side reactions to occur in the n-BuLi feed arm where localized n-BuLi concentration is high, which accounts for the lower yield/selectivity observed at Re above 4800. Similar observation is made by Kockmann and co-workers²⁶ where the segregation index is increased for similar range of Reynolds number used in T-mixer.

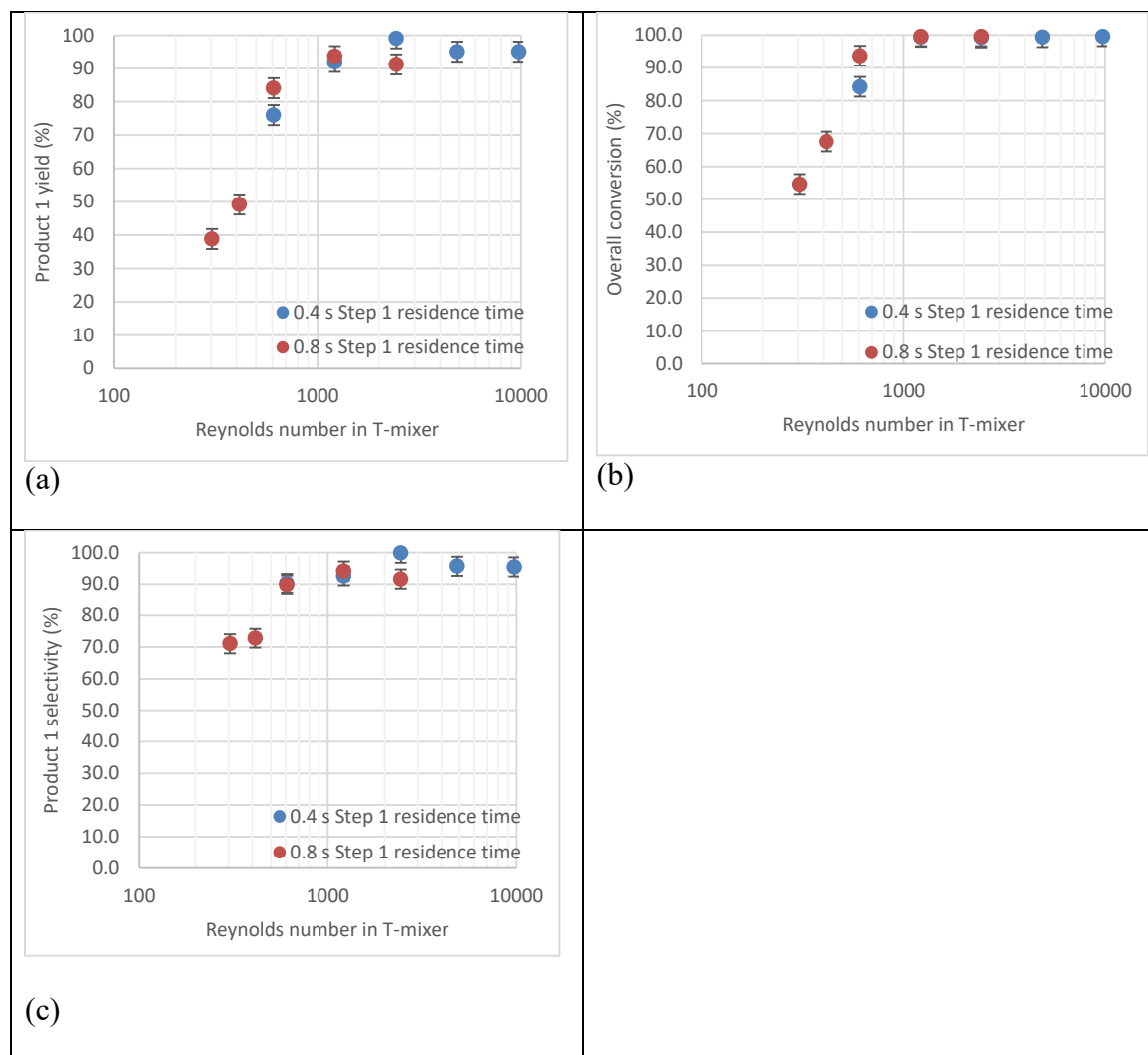


Figure 4 (a) Product 1 yield; (b) Overall conversion; (c) Product 1 selectivity against Step 1 combined flow speed in terms of Reynolds number in the first T-mixer.

3.3. Development of the SDR flow process

3.3.1. Mode of DMF addition

The DMF feed is added close to the edge of the disc (4.5 cm radial distance away from the center of the disc) where the mixing performance should be better compared to other parts of the disc. While the residence time of Step 2 on the disc is expected to be even shorter than Step 1 as it has only a radial distance of 5 mm to mix and react, Step 2 reaction is expected to be faster than Step 1.¹⁴ Thereafter, the reaction mixture flies off the disc and splashes onto the housing

1
2
3 wall which is, in fact, a form of mixing as well. Theoretically, SDR offers relatively better
4
5 mixing for Step 2 reaction than Step 1 provided that the DMF feed contacts the disc as a
6
7 continuous stream rather than dropwise. Through visual observation, a minimum flow rate of 2
8
9 mole equivalent (0.06 mL/s) of DMF is required for the lowest Step 1 combined flow rate of 1.3
10
11 mL/s to ensure a continuous stream of DMF from the feed pipe.
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15
16

17 3.3.2. Position of n-BuLi feed

18
19 Theoretically, the mixing of the amide **1** and n-BuLi feeds could be improved by moving one
20
21 of the feed (e.g. n-BuLi) away from the center of the disc, where the mixing is poor, to a higher
22
23 radial position where the film thickness is smaller.¹⁵ However, the result obtained for n-BuLi
24
25 feed placed 2.5 cm from center of the disc were worse than position at center of disc (Table 5).
26
27
28

29 The poorer overall conversion could be explained by the reduction in residence time as the n-
30
31 BuLi feed moves 2.5 cm closer to the edge of the disc. The increase in impurity might be the
32
33 result of increased n-BuLi to amide **1** stoichiometric ratio as the n-BuLi feed stream is not evenly
34
35 distributed over the entire disc but expected to be concentrated at the point of contact. As
36
37 demonstrated by Boiarkina²⁷ in dye experiments with well-defined and minimal spreading path
38
39 lines of the injected dye across the radius of the disc. It is evident from Table 6 that higher n-
40
41 BuLi stoichiometric ratio increases formation of impurity.
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47 **Table 5** Effect of position of n-BuLi feed on reaction profile

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Position of n-BuLi feed	Flow rate (mL/s)	Disc speed (rpm)	Product 1 yield (%)	Overall conversion (%)	Impurity* (%)
Center of disc	1.3	1400	87	97	10

2.5 cm away from center of the disc	1.3	1400	66	90	24
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(*) % impurity = % overall conversion - % product 1 yield

Table 6 Flow rate of 1.3 mL/s and disc speed of 1400 rpm

n-BuLi mole eqv	Product 1 yield (%)	Overall conversion (%)	Impurity* (%)
0.9	84	85	1
1.3	87	99	12
1.6	77	99	22

(*) % impurity = % overall conversion - % product 1 yield

3.3.3. Effect of SDR coolant temperature

The coolant temperature dictates the disc surface temperature in the SDR. Figure 5 shows that the yield is only marginally affected by the coolant temperature. Similar explanation as in the T-reactor can be applied where the effect of temperature is limited by the short contact time between the reagents and the disc. Although compared to the T-reactor, the SDR is expected to have a better heat transfer capability where the coolant is supplied directly beneath the metal rotating disc which has a relatively large surface area for heat transfer, the SDR has even shorter residence time and thus shorter exposure time to the higher surface temperature than the T-reactor.

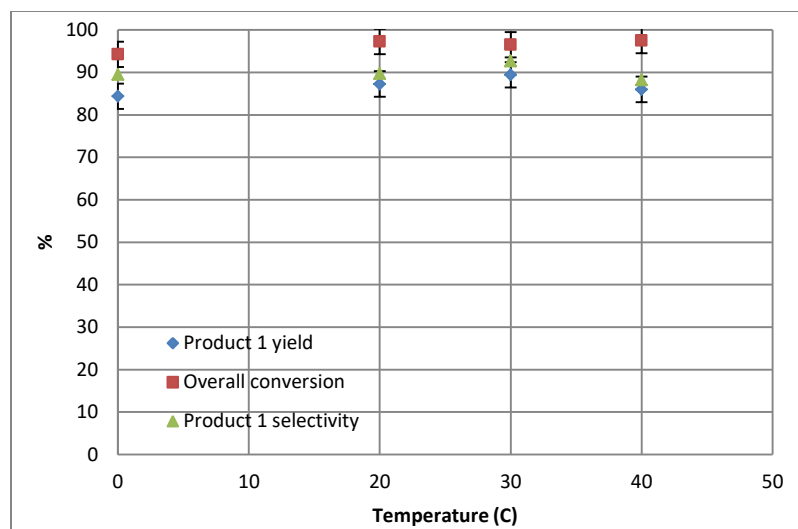


Figure 5 Effect of circulated bath temperature under constant residence time (0.4 s), total flow rate (1.2 mL/s) and disc speed (1,400 rpm).

3.3.4. Effect of total flow rate (Step 1)

Figure 6 shows a steady decrease in the product 1 yield and overall conversion with the increase in flow rate from 1.2 to 5 mL/s at a disc speed of 1,400 rpm.

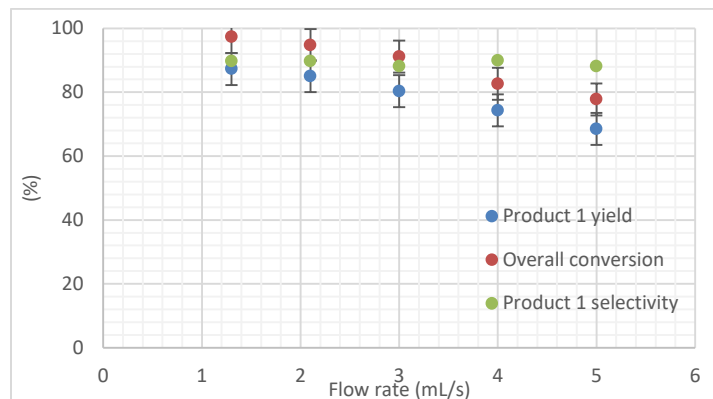


Figure 6 Effect of total flow rate (Step 1) under constant disc speed of 1,400 rpm.

Under the same disc speed, Figure 7 shows the corresponding residence time for the flow rates in Figure 6 at 1,400 rpm. The residence time decreases with increasing flow rates, from 0.15 s at lowest flow rate to 0.05 s at the highest flow rate. It is known that ortho-lithiation reaction time is

very fast especially at high temperature, so the reaction is most likely mixing limited in this regime. The micromixing time reported by Hinrichsen¹⁵ using similar operating conditions and disc size, is in the range of 0.125 to 0.02 s. If a conservative estimate of 0.125 s is taken to be the average micromixing time regardless of flow rate and disc speed, Figure 7 shows that for disc speed of 1,400 rpm and flow rates above 1.2 mL/s, the corresponding residence times could be shorter than the micromixing time (represented by the dotted line). This suggests that the mixing controlled reaction might be indirectly limited by the short residence time. Therefore, the longer residence time benefits the mixing as it allows more time for molecular contact. This trend is similarly observed in the T-reactor with low flow rates.

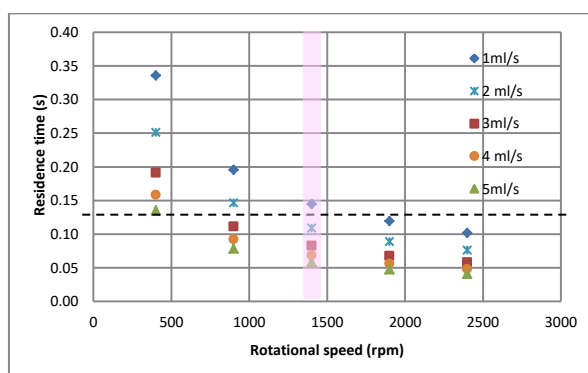


Figure 7 Estimated residence time²⁸ of Step 1 on the disc at different flow rates and disc speeds. Data within the pink area represents the corresponding residence times at 1,400 rpm.

Although the SDR residence time can be extended by reducing the disc speed, the mixing intensity might be compromised even further. Compared to the T-reactor which offers residence times of 0.2 to 3 s, the estimated range of residence time of 0.05 to 0.15 s used in the existing SDR is much shorter. The shorter residence time on the SDR is more likely to minimize over-reaction at the expense, however, of insufficient mixing.

3.3.5. Effect of disc speed

Attempts were made to improve the mixing and thus, the reaction dependency on residence time. From Figure 8 and Figure 9, it can be inferred that the product **1** yield and overall conversion are inversely proportional to the film thickness for flow rates at 3 and 5 mL/s. In the lower disc speed range, typically between 400 and 1,400 rpm, the film thickness decreases considerably and the corresponding yield increases significantly. Beyond 1,400 rpm, there is only a marginal decrease in film thickness from about 30 to 20 μm which is accompanied by a minimal increase in yield. This seemingly direct correlation between film thickness decrease and yield increase highlights more rapid mixing and mass transfer taking place across the reduced path length of thinner films.

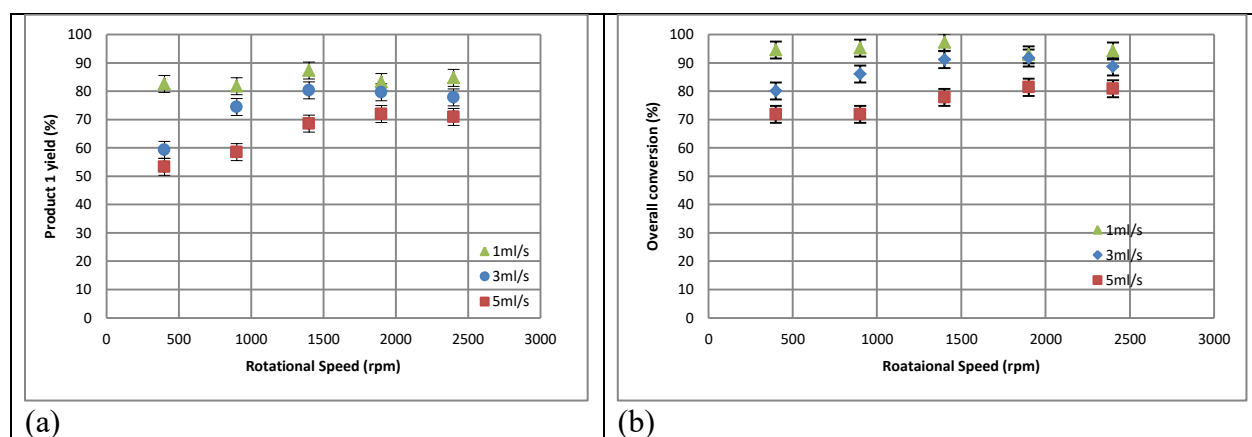


Figure 8 (a) Product **1** yield; (b) overall conversion against disc speeds of 400 to 2400 rpm at different flow rates.

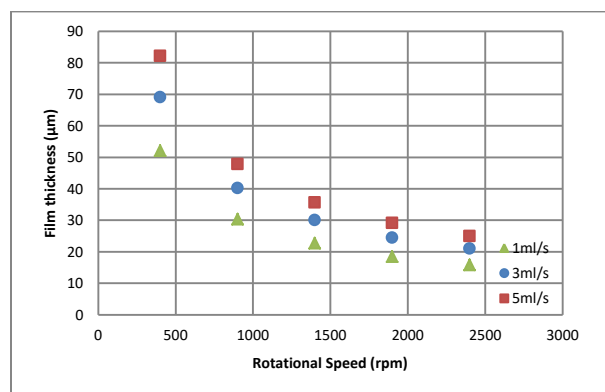


Figure 9 Estimated film thickness¹⁶ at different disc speed at constant total flow rates.

The convergence of the film thickness profiles at high disc speeds in Figure 9 also matches the product **1** yield trends seen in Figure 8 (a), suggesting that the limit of highest mixing/mass transfer has been reached for the process under consideration. Similar convergence profiles were observed at high disc speeds in micromixing studies conducted in the SDR.²⁸ This observation is in agreement with the findings made by Hinrichsen¹⁵ that the micromixing segregation index is directly correlated to the calculated film thickness.

The ortho-lithiation reaction was carried out in three reactors and the operating conditions of the best runs are summarized in Table 7. The experience gained from the experiments should provide adequate basis to illustrate the critical differences in performance that would be expected between batch and flow processes at industrial scale. Table 7 presents the operating conditions that would be used in the batch and flow process designs.

Table 7 Highest yield obtained in the different reactors and their respective operating conditions.

	STR	T-reactor	SDR
Coolant temperature (°C)	-80 °C	17 °C	17 °C
Yield (%)	96	99	87
Amide 1 concentration (M)	0.4	0.4	0.4
Step 1 combined flow rate (mL/s)	-	1.2	1.2
Residence time (s)	Mins (depends on dosing rate)	~0.4 s	~0.14 s
Micromixing time (s)	Seconds	~3 x10 ⁻⁴ s	0.125-0.02 s ¹⁵
BuLi mole eqv	1.2	1.2	1.2
DMF mole eqv	1.3	2	2

3.4. Design of the stirred tank reactor, T-reactor and SDR reaction systems for 3 tons per year production.

Having obtained laboratory data for the three process technology options we proceeded to generate designs for operation at a nominal 3 tons per year scale. For each technology we

considered whether the laboratory data were representative of what could be achieved at the larger scale.

For the batch STR, due to lack of suitable large equipment that can provide a proper cooling system ($-80\text{ }^{\circ}\text{C}$), we were unable to perform ortho-lithiation at our designed industrial scale of 28 L. However, it would still be possible to design the STR batch process by making some realistic assumptions based on the laboratory results at 50 mL Multi-max TM scale. It was identified that the reaction is most sensitive to temperature which is directly controlled by the n-BuLi dosing rate. To ensure the cooling capacity of the reactor is sufficient to cope with the n-BuLi dosing rate, a conservative overall heat transfer coefficient value is assumed. In addition, good mixing is required to avoid temperature gradient. The power dissipation of the 50 mL Multi-max TM at its maximum achievable agitation speed is used as a basis for providing sufficient mixing required for the 28 L reactor. The refrigeration method is one of the biggest difference between the laboratory Multimax TM and designed industrial process. The vapor-compression refrigeration system is selected for the large scale cryogenic reactor design which is based on highly idealized model.

A two-stage selected cascade system schematic is shown in Figure 10. The refrigeration system consists of two compressor units, two heat exchangers, two throttles and an evaporator is required to achieve a refrigeration temperature of $-80\text{ }^{\circ}\text{C}$. Refrigerants R-32 and R-23 are selected for the cascade cycle to provide maximum thermodynamic efficiency and recycled after each batch. An ideal cycle model was assumed, taking into account the compressor in the cryogenic reactor is driven by an electric motor with an efficiency of 0.72. The utilities consumed will be mainly for compressor duties, pumping, agitation and chilled water for

condensation. In order to achieve similar mixing intensity, the agitation power of the large scale STR is designed to have similar agitation power as the bench scale of 0.053 W/kg.

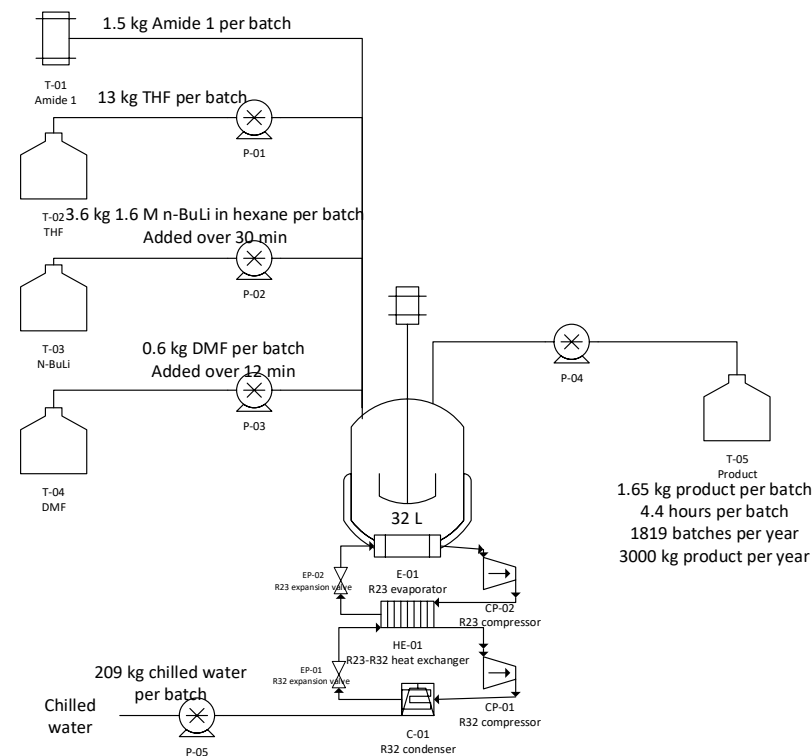


Figure 10 Schematic process diagram for batch process.

For both the T-reactor and the SDR flow processes, their process designs would be based on the actual laboratory operating conditions (flow rate, temperature, residence time, etc.) used in their best runs in Table 7 that are able to deliver an annual production of about 3 tons per year. This provides more realistic operating conditions on the flow reactors, rather than artificially try to predict the yield at other operating conditions. One point to note is that for all the flow experiments conducted either in the T-reactor or the SDR, the maximum duration of the run is about 5 minutes due to volume limitation of the syringe pump. However, the large scale design requires the run duration to be extended to 8,000 h.

Although there was no clogging in the T-reactor experiments as the runs performed were very short, there could be a possibility of agglomeration of the precipitate²⁹ over time and result in clogging of the mixing chamber. One possible option to get around this problem is to build in several T-reactors that can be easily switched to another when pressure build up is sensed. The clogged T-reactors can then be disposed and replaced swiftly as the T-mixers and tubes are relatively cheap. In this way, sudden disruption to the process due to clogging and maintenance of the T-reactor can be avoided entirely.

Even though a small amount of lithium salt was observed on the surface of the disc after the experiments, the SDR is clearly less prone to clogging. The SDR maintenance can be scheduled regularly without the worry of sudden severe pressure drop as seen in the T-reactors.²⁹ Another operational advantage of the SDR is the variation in rotational speed which offers an additional degree of freedom as the disc speed can be controlled independently of the flow rate to achieve target mixing intensity without affecting the throughput.

One common drawback in the flow processes is the less efficient method to prepare the amide **1** solution as additional equipment are required to dissolve the amide **1** in THF. The respective reactor setups are shown in Figure 11 and Figure 12. 32 L of amide **1** solution (0.4 M) will be prepared in a 41 L mixing tank (M-01) in batch mode which will provide 8 hours of amide **1** solution supply for the T-reactor. To ensure continuous supply of the amide **1** solution, two mixing tanks are required to alternate between each other when one is consumed. Similarly, two product storage tanks (T-05) will be required.

For the T-reactor system (Figure 11), the utilities used will be mainly the electricity for silicone oil bath cooling, pumping and agitation for mixing tanks. To avoid evaporation of butane during the reaction, a back pressure of 2 bars is applied.

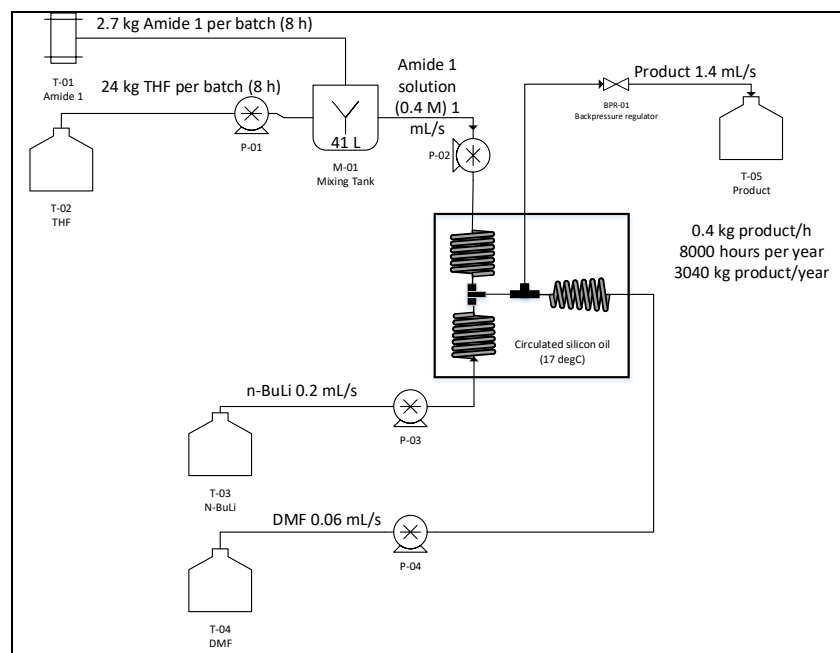


Figure 11 Schematic process diagram for T-reactor flow process.

For the SDR flow process (Figure 12), the utilities used will be mainly the electricity for rotating the disc, silicone oil bath cooling, pumping and agitation for mixing tanks. No backpressure is applied in this system, so butane is expected to evaporate from the surface of the disc and which will be diluted by the continuous supply of nitrogen gas. The mixture of gas then escapes together with the final reaction mixture through the sink underneath the SDR. Although argon gas was used in the experiment, nitrogen gas can also be used and is considered in the reactor design.

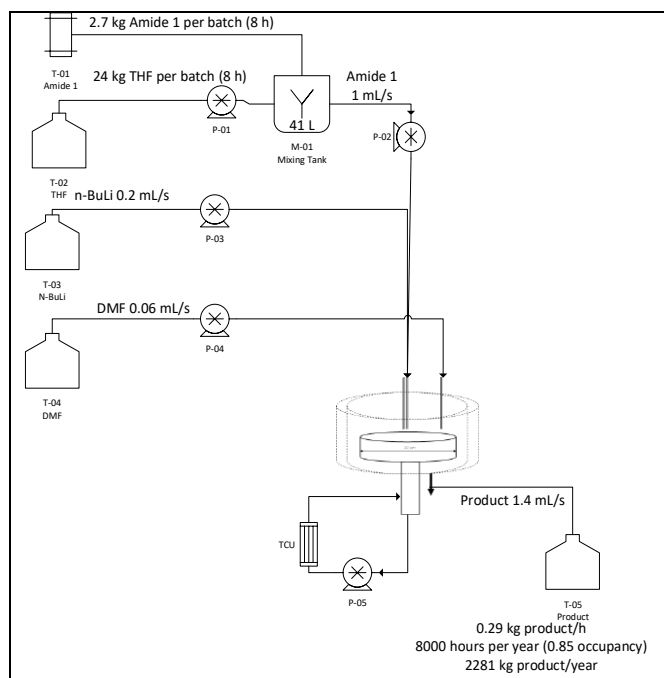


Figure 12 Schematic process diagram for SDR flow process

The following general design assumptions were made:

- 1) No loss of product **1** yield due to workup, assume all product **1** can be recovered. (workup is excluded from the study)
- 2) All reactors are assumed to be air and moisture free during the course of the reaction.
- 3) At the end of the reaction, butane gas (byproduct) is assumed to be diluted and discharged via nitrogen purge.
- 4) All chemicals are at ambient temperature which is at 20 °C.
- 5) Concentration of purchased n-BuLi in hexane is always 1.6 M.
- 6) Total number of operation hours per year in a plant is 8000.
- 7) T-reactor and SDR reach steady state in less than a minute observed from experiment data, assume insignificant product **1** loss due to unsteady state flow during start up and shut down.

- 8) No observable degradation of product **1** after addition of DMF during storage based on GC.
- 9) Pump efficiency assumed to be 50 %.
- 10) Specifications of purchased raw materials is assumed as in Table 8.

Table 8 Specifications of the raw materials

Raw materials	Specifications
4-chloro-N,N-diisopropylbenzamide (amide 1)	Solid, >99% pure
n-BuLi in Hexane	Liquid solution, 1.6 M
Tetrahydrofuran (THF)	Liquid, anhydrous, 99.9% stabilized with BHT
Dimethylformaide (DMF)	Liquid, anhydrous, 99.8%

3.5. Comparisons of sustainability performance

Based on the above process designs, we evaluated the sustainability performance in terms of volume, mass and energy efficiencies and estimated the expected operating (OPEX) and capital cost (CAPEX) respectively (Table 9). The reactor volume in the flow processes are smaller than the equivalent batch process because of the shorter residence time. In terms of the footprint of the major equipment, the T-reactor and SDR process are only 20 % of the batch equivalent.

Maximum processing inventory at any point of time for batch process includes the stirred tank reactor volume. As for the T-reactor and the SDR flow processes, it refers to the volume of the reactor and the piping of the reactor system. The mixing tanks are excluded from the process equipment as they do not deal with n-BuLi and are not involved any reactions; they are instead considered as part of the storage unit. On this basis, the T-reactor and SDR flow processes provide much smaller processing inventory as compared to batch process. This would provide significant safety benefit especially when dealing with hazardous chemical like n-BuLi.

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3 With the T-reactor operating at a flow rate of 1.3 mL/s, it is able to handle the throughput of a
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5 32 L stirred tank reactor which would require strict safety measures to be in place. However, one
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7 possible safety concern when operating the flow reactors could be the incomplete quench of n-
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9 BuLi during unsteady state flow which may occur during the reactor start-up or shut down
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11 phases. This could lead to unreacted n-BuLi to exit from the flow reactors and get into direct
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13 contact with water during the downstream separation process. This scenario could be avoided by
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15 starting the n-BuLi feed pump last during start-up and stopping it first during shut down, this
16
17 ensures sufficient quantities of amide 1 and DMF are present to react with and quench n-BuLi.
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21 Comparing the process safety considerations of the T-reactor and SDR, the T-reactor presented
22
23 a higher risk of leakage of reaction mixture if the system was pressurized due to clogged
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25 channel. This is an unlikely situation in SDR where even if there was precipitation on the disc it
26
27 would not affect the system pressure. To minimize the danger of n-BuLi leaking from the T-
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29 reactor into the environment, silicon oil was used as coolant in the circulated cooling system as
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31 its moisture content is lower (especially at 20 °C -minimum condensation) and it is less reactive
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33 towards n-BuLi.
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39 As for the SDR, the major safety concern lies with the presence of vapour space in the reactor,
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41 unlike T-reactor, the butane gas produced in SDR is allowed to escape from the liquid film and
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43 the large surface area of the liquid film also promoted evaporation of the volatile solvents. If
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45 there was failure in the inert gas supply or insufficient inert gas to dilute the organic vapour,
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47 there would be accumulation of flammable vapour in the SDR vapour space. This risk can be
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49 mitigated by setting up an alternative inert gas supply which can be placed in operation if failure
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51 in primary inert supply was detected. Moreover, the SDR reactor volume is much smaller than
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the batch reactor volume and this put a limit to the maximum quantity of flammable vapour that can be accumulated, so it can be diluted fairly quickly and has a less catastrophic consequence.

There is hardly any difference in total material efficiency between the STR and T-reactor because both processes have similar product **1** yield. The SDR is less material efficient due to lower reaction selectivity. Even though the quantity of DMF used in the T-reactor and SDR flow processes is slightly higher than in the batch process, it appears that its impact on the total material efficiency is minimal.

Table 9 Comparisons of sustainability metrics between STR, T-reactor and SDR process at design scale of about 3 tons per year product **1**.

	STR	T-reactor	SDR
Operation time fraction	0.5	1	1
Throughput (kg product/h)	0.38	0.38	0.29
Processing equipment footprint ratio	1	0.2	0.2
Max processing inventory at any point of time (L/kg product/h)	59	0.01	0.06
Total material efficiency (kg product/kg material*)	0.087	0.090	0.079
Material efficiency (%)	-	4	-8
Total energy efficiency (kJ/kg product)	3,956	1,321	2,173
CAPEX (USD/kg product)	48	31	40
Economic savings in CAPEX (%)	-	36	16
OPEX (USD/kg product)	456	406	466
Economic savings in OPEX (%)	-	11	-4

(*) kg material consists of masses of amide **1**, n-BuLi, DMF and THF.

Figure 13 shows the energy consumption breakdown of the processes. Compressor duties in the two-stage cascade refrigeration system consumes the most energy to maintain the reaction temperature at -70 °C. Although the two-stage cascade refrigeration system is more energy efficient than direct cooling with electricity, the energy required in the batch process is still much higher than in the flow processes because it needs to maintain at a very low temperature. In addition, the pumping duty required in batch process is also much higher than in the flow

processes because the material flow rate is higher than in the flow reactors where the flow rate is averaged and becomes smaller. The T-reactor flow process gives the best energy efficiency where the overall energy consumption is about 65% lesser than the batch equivalent. The avoidance of the use of cryogenic temperature in the flow reactors resulted in tremendously energy savings. The sources of energy usage for the T-reactor and the SDR processes are similar with the exception of additional energy required for disc rotation in the SDR and extra pump duty needed to overcome the backpressure (2 bars) in T-reactor. The SDR process requires about 50% more energy than the T-reactor to account for the disc rotational energy which consist of the rotational energy of the dry disc, overall kinetic energy supplied to the fluid and frictional energy dissipation of the fluid on the disc.³⁰

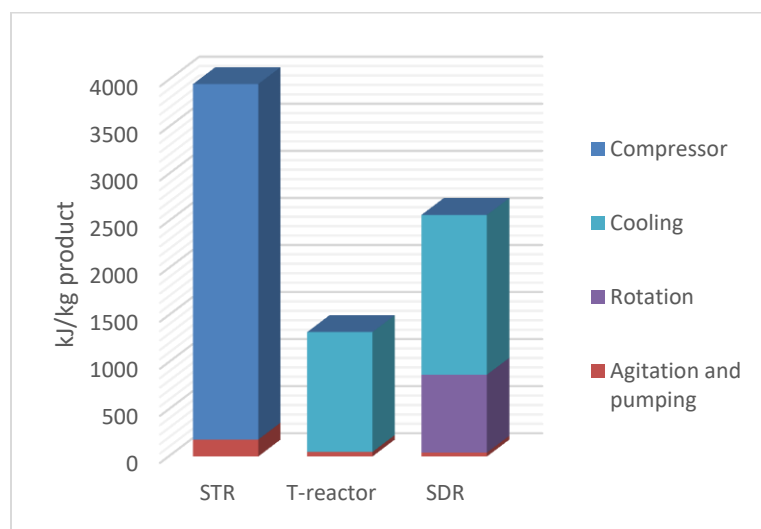


Figure 13 Breakdown of the energy consumption.

The calculation of the operating cost (OPEX) in Figure 14 is based on the cost of raw materials and utilities which consists of electricity, chilled water and nitrogen cost. It is found that the raw materials cost represents the bulk of the OPEX. Amide **1** is the most expensive reagent among

the chemicals used. The cost analysis shows cost saving of 10 % for the T-reactor in OPEX which is mainly contributed by the increased in product **1** yield (99 %) as compared to 96 % in the STR. Despite lowering the energy consumption by more than 50 %, the SDR incurred a higher OPEX than the STR due to its lower product yield under the conditions tested in this study. The cost savings from reduced energy consumption is meagre compared to the cost of amide **1** due to the lower yield in the SDR (86 %). The reaction yield will also affect the downstream process (workup) which is critical to the overall process cost. A higher yield could mean a less tedious workup and waste treatment procedure that leads to further cost reduction. However, the impact of yield on subsequent workup is not included in the scope of our current study.

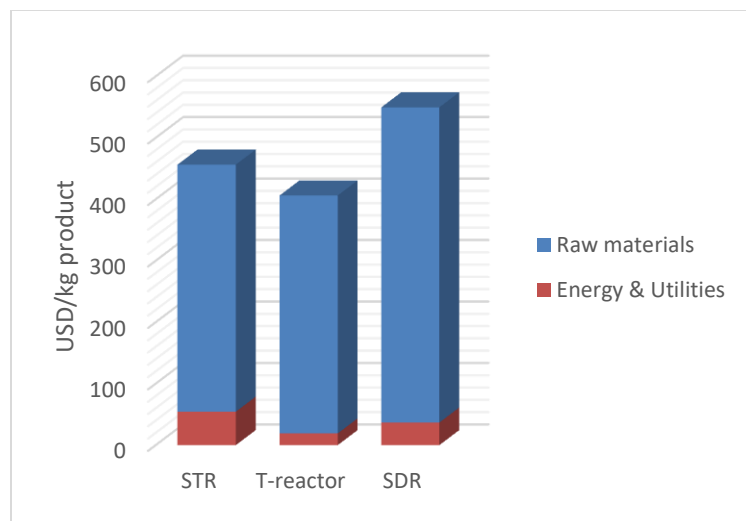


Figure 14 Cost breakdown of the OPEX.

A rough estimation of the capital cost investment is done based on new major equipment and setup required to operate the processes respectively. Costing of common equipment like the storage vessels, heat exchangers, compressor, etc. is obtained from online suppliers. For the STR, the cryogenic reactor makes up more than 50 % of the CAPEX. For the flow reactors, the

increased proportion of tanks in CAPEX is due to the additional mixing tanks and product storage tanks which are required to ensure continuous production. The CAPEX of the T-reactor includes the reactor and an open silicone oil temperature controlled circulated bath. The T-reactor is assembled in-house so it is relatively cheap considering only the cost of T-mixers and tubes which is insignificant compared to the cost of the temperature controlled circulated bath. The SDR is currently commercially unavailable so assumption is made regarding its selling price which includes the cost of material (316 stainless steel), electric motor, labor and frame cost. Since reaction can be performed at ambient temperature in flow reactors, costly refrigeration equipment (e.g. compressors, heat exchangers, condenser and evaporator) and cold resistant reactor vessel could be avoided which leads to lower CAPEX in flow reactors compared to STR as shown in Figure 15.

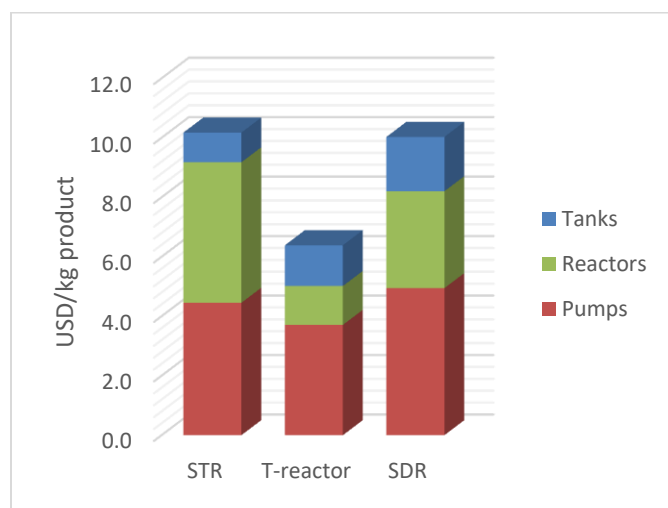


Figure 15 Cost breakdown of the CAPEX.

4. Conclusion

The feasibility of performing the ortho-lithiation reaction in the T-reactors and the SDR at ambient temperature has been demonstrated. The conventional method is to operate the reaction

at -70 °C in a fed-batch mode which is challenging to scale up. By performing the reaction in flow reactors, similar yields were achieved with a much shorter residence time at ambient temperature. Compared to batch process, significant process intensification is achieved in the flow reactors which demonstrate higher energy efficiency, better volume efficiency, smaller processing inventory, smaller equipment footprint.

The performance of the T-reactor is particularly outstanding among the three reactors leading to much lower reactor investment and operating cost. Based on these promising results, the use of T-reactor presents a commercial viable alternative to the conventional batch processing.

The SDR also performs well and brings additional energy-saving benefits. Further optimization of its operating conditions offers distinct potentials of improvement in the desired product yield to a level similar to the T-reactor. More importantly, the free surface film characteristics of the SDR, in contrast to the fully enclosed volume of the T-reactor, could render the SDR more advantageous if other processing capabilities were desirable- for example, handling a reaction with solid formation or requiring rapid heat removal through evaporation or formation and removal of gas that the T-reactor cannot do.

Our future work will involve the study of the whole process including workup for the batch and flow processes. The reaction yield will affect the downstream processes which is critical to the overall process cost. The results of the evaluation will be reported separately.

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Notes

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